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# A Novel Enantioselective Preparation of α-Fluoro-β-Keto Acids[1]

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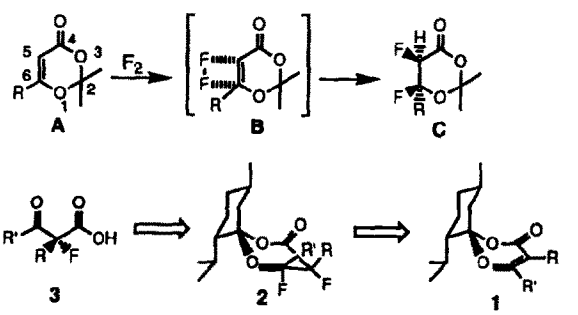
**Abstract:** A two-step method for the enantioselective preparation of α-fluorinated β-keto acids from 1,3-dioxin-4-ones having *l*-menthone as the chiral auxiliary at the 2-position is described. The method consists of fluorination of the dioxinones by molecular fluorine and solvolytic cleavage of the acetal function.

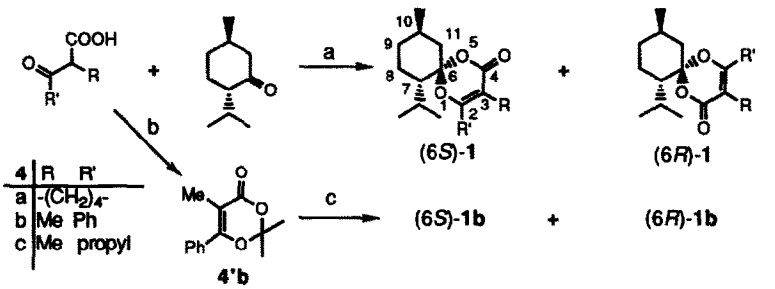
We have been interested in using chiral spirocyclic dioxinones as synthons of enantiomerically pure compounds (EPC)[2] and have so far succeeded in the EPC synthesis of Corey lactone[3] and iridoids[4] by photo[2+2]cycloadditions and carbocyclic C-nucleosides[5] by Diels-Alder reactions. As pointed out originally by Demuth in his elegant synthesis of (+)-grandisol using the photocycloaddition as the key step,[6] the successful use of these chiral dioxinones as $_{\pi}2$ components in the above mentioned pericyclic reactions is due to the sofa-conformation (e.g. **1**) of the dioxinone ring, which could accept other components (alkenes and dienes) from the more exposed isopropyl-side.

In this communication, we report an enantioselective preparation of α-fluorinated β-keto acids (**3**) from the chiral dioxinones (**1**) via the *cis* addition of molecular fluorine to give the adduct (**2**) followed by cleavage of the acetal function. This strategy is based on the known *cis*-addition of fluorine to the dioxinone C-C double bond (**A**→**C**)[7] and on the proposed mechanism involving the square-type complex (**B**)[8] as the intermediate accounting for this selectivity. The mechanism suggests that the C-C double bond of the dioxinones (**1**) would accept molecular fluorine, just like as the above-mentioned pericyclic reactions (Diels-Alder and photo[2+2]-cycloaddition reactions), from the less hindered isopropyl-side. The α-acylated derivatives (**3**) of α-fluoro-alkanoic acids thus obtained have been used as synthetic intermediates of a variety of fluorinated organic molecules,[9] and hence, this work also would provide new methodology for the EPC synthesis of fluorinated organic molecules.




Scheme 1

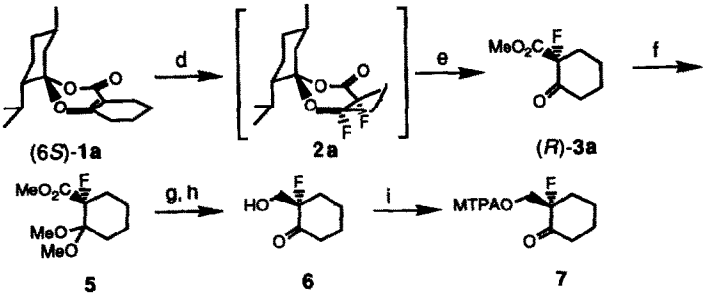
As the substrates, three dioxinone all having (*S*)-configuration at the 2-position were synthesized from *l*-menthone by the established method.[10, 11] Thus, taking **1a** as a typical example, the mixture (*ca.* 12:1) of two diastereoisomers of the dioxinone obtained in 58% yield by reaction of the *l*-menthone with the cyclohexanone (**4a**) was separated by silica gel column chromatography to give (6*S*)-**1a** as the less polar product. Though (6*S*)-**1c** was obtained from **4c** in the same manner, (6*S*)-**1b** was obtained in satisfactory yield (53%) only by the trans-ketalization of the 6-phenyldioxinone **4'b**[10] with *l*-menthone. In this case, the ratio of two diasteromers (6*S*)-**1b** and (6*R*)-**1b** was *ca.* 1:1. Determination of the absolute structures of each diastereomer was accomplished by analysis of 500 MHz $^1$H-NMR spectra of each diastereomer according to our general classification method.[12]




*Conditions*: a) $Ac_2O$, catalytic $H_2SO_4$, neat, 5 °C,15 h; b) acetone, $Ac_2O$, catalytic $H_2SO_4$, neat, 5 °C,15 h ; c) *l*-menthone, neat, 150 °C, 4 h

Scheme 2

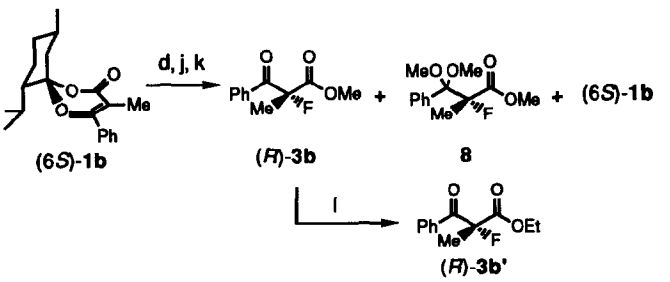
When (6*S*)-**1a** {mp 86.5-90 °C, $[\alpha]_D^{24}$ +32.8 (*c* 1.20)}[13] was reacted with molecular fluorine,[14] the adduct (**2a**) was formed. Due to its instability, the crude product was treated directly with potassium carbonate in methanol to give the fluorocyclohexanone {**3a**: bp 75 °C (1 mm), $[\alpha]_D^{21}$ +107.8 (*c* 1.00)}. In order to determine the e.e., the product **3a** was converted to the Mosher's ester **7**. Analysis of 500 MHz $^1$H-NMR spectrum of **7** revealed that the e.e. was ≥98%. This is consistent with the expected high d.e.[(6*S*)-**1a**→**2a**].




*Conditions*: d) 5%-$F_2/N_2$, acetonitrile, -30 °C; e) $K_2CO_3$, MeOH, 5 °C, 30 min, 30% from **1a**; f) $CH(OMe)_3$, catalytic *p*-TsOH, MeOH, reflux, 5 h, 79%; g) $NaBH_4$, MeOH, 50 °C, 3.5 h; h) 10%-HCl, acetone, r.t., 10 min, 53%; i) MTPA, DCC, 4-dimethylaminopyridine, $CH_2Cl_2$, r.t., 12 h, 60%

Scheme 3.

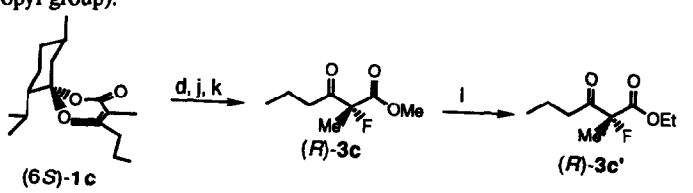
In order to determine its absolute configuration, we then investigated the same reaction sequence using (6*S*)-**1b** {mp 158-159 °C, $[\alpha]_D^{20}$ +124.0 (*c* 1.06)} as the substrate. After examining a variety of conditions of the hydrolysis step for improvement in the overall yield, the following conditions have been found to be the best. Thus, the adduct **2b** was treated with hydrogen chloride/MeOH followed by diazomethane to give **3b** {bp 59 °C (2 mm), $[\alpha]_D^{22}$ -85.0 (*c* 1.00, MeOH)} in 43% yield. In this case, the acetal **8** {bp 72 °C (2 mm), $[\alpha]_D^{22}$ -18.8 (*c* 2.00, MeOH)} and the starting material (6*S*)-**1b** were obtained in 13% and 31% yields, respectively. The conversion of the methyl ester (*R*)-**3b** to the known chiral ethyl ester (*R*)-**3b'** {bp 82 °C ( 2.5 mm), $[\alpha]_D^{22}$ -85.4 (*c* 1.00, MeOH): lit[15] bp 102-104 °C (4 mm), $[\alpha]_D$ -84.8 (*c* 1.79, MeOH)} has revealed not only that the absolute configuration at chiral center is *R* but also that its e.e. is almost 100%.




*Conditions*: d) 5%-$F_2/N_2$, acetonitrile, -30 °C; j) HCl, MeOH, 5 °C, 30 min; k) $CH_2N_2$, ether; l) catalytic *p*-TsOH, EtOH, reflux, 29 h, 54%

Scheme 4.

Finally, (6*S*)-**1c** {$[\alpha]_D^{24}$ +10.2 (*c* 1.00)} was used in the same reaction sequence. The addition product when treated with hydrogen chloride/MeOH followed by methylation with diazomethane gave (*R*)-**3c** {bp 76 °C (62 mm), $[\alpha]_D^{23}$ -28.8 (*c* 2.39, MeOH)} in 52% yield. Comparison of $[\alpha]_D$ of the corresponding ethyl ester (*R*)-**3c'** {bp 88 °C (24 mm), $[\alpha]_D^{22}$ -31.1 (*c* 2.50, MeOH): lit[15] bp 65-67 °C (19 mm), $[\alpha]_D$ -42.6 (*c* 2.04, MeOH)} shows that the e.e. is *ca.* 73%. Evaluation of the e.e. by means of NMR spectroscopy using [Eu(hfc)$_3$] as the shift reagent also gave the same result. The low e.e. may be due to the flexibility of the substituent (the n-propyl group).[16]




Scheme 5

Thus, it is established that the addition of fluorine has occured from the isopropyl-side, irrespective of the substituents on 5- and 6-positions of the dioxinone ring.

The present method for the synthesis of enantiomerically pure 2-acylated 2-fluoroalkanoic acids (**3**)[17,18] has the following three advantageous features: 1) high d.e. for the addition step and hence, high e.e. of **3**, 2) applicable to a variety of substituted dioxinones and hence, to the conversion of a variety of α-substituted β-keto acids (racemic) to the corresponding α-fluorinated ones (EPC),[19] and 3) since the (6*S*)-dioxinones **1**

afford (*R*)-alkylated acids (**3**) via the isopropyl-side addition products, one can readily settle the synthetic plan for the enantioselective preparation of any kind of α-substituted α-fluoro-β-keto acids.

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11. M. Sato, K. Sekiguchi, H. Ogasawara and C. Kaneko, *Synthesis*, **1985**, 224.
12. So far, we and others have synthesized many chiral spirocyclic dioxinones and determined the absolute configuration of several isomers by X-ray crystallographic analysis.[3,4,6] After examining their properties, two characteristic features which distinguish the two diastereomers have been found: 1) in $^1$H-NMR spectra, the signals of $C_{11}$-$H_{axial}$ and the methine proton in the isopropyl group of the 6*S* -isomers appear in a higher field than those of the 6*R*-isomers and 2) on chromatography by silica gel, the 6*S*-isomers are, without exception, less polar than the 6*R*-isomers.
13. All new compounds exhibited satisfactory spectroscopic (NMR, IR) and combustion or high-resolution mass spectral analytical data. Unless otherwise noted, specific rotations were measured in $CHCl_3$.
14. Detailed experimental procedure for the fluorination, see reference 7.
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16. Due to the flexibility of propyl group, the terminal methyl group in it would occupy the less hindered isopropyl-side of (6*S*)-**1c**. In such conformation, the isopropyl-side attack of $F_2$ may be prohibited in some extent in comparison to the cases for the corresponding **1a** and **1b**.
17. To the best of the present authors' knowledge, only the β-keto acids having 2-methyl group have been synthesized from the corresponding malonic acid monoesters by reaction with alkyl (or aryl) cuprates.[15] This method is applicable to the preparation of related β-keto acids, if the corresponding malonic acid monoesters are available.
18. Three methods for the synthesis of optically active monofluorinated 2-substituted malonic half esters were reported: a) T. Kitazume, T. Sato and J. T. Lin, *J. Org. Chem.*, **51**, 1003 (1986); b) M. Ihara, T. Kai, N. Taniguchi and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, **1990**, 2357; c) M. Sato, N. Kitazawa and C. Kaneko, *Heterocycles*, **33**, 105 (1992).
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